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Short Review

The Role of Gene Therapy as an Application of Biotechnology in the Treatment of Lung Cancer

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1. Introduction

Our lungs are amazing organs that take up a large volume of air daily. Inhaled air contains small particles and aerosols, and lungs require them to guard against inhaled viruses, germs, and numerous respiratory infections by producing the mechanical force of breathing. The specialized lung environment is protected by complex immune interactions[1].

Lung disease refers to several disorders that prevent the lungs from working properly and can affect the respiratory function of the lungs[1]. Lung cancer is one of the world's most frequent lung disorders. Despite recent advancements, this disease remains the leading cause of cancer deaths[2].

Most of the field of gene therapy holds promise for a variety of innovative treatments that could be important in preventing cancer deaths[3]. Gene therapy was first intended to cure monogenetic disorders. Due to the presence of various genetic faults and alternations in the molecular profile that occur throughout the disease, it is impossible to replace all damaged genes in cancer. Multiple gene therapy procedures have been used in order to overcome these challenges, including immune stimulation, transfer of suicide genes, inhibition of cancer driver genes, substitution of tumor suppressor genes that may mediate apoptosis and angiogenesis inhibition, radiation, and chemotherapy. Studies have shown that some of these treatment methods have worked successfully in patients with non-small cell lung cancer[4].

Non-small cell lung cancer, which affects 85% of patients, and small cell lung cancer, which affects 15% of patients, are the two main types of lung cancer. The World Health Organization classifies NSCLC into three types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[5]. The most important cause of death from cancer is non-small cell lung cancer[4]. Squamous cell carcinoma of the lung develops from the epithelial cells of the main and lobular bronchi, whereas adenocarcinoma arises in peripheral lung tissue and originates from the epithelial cells of the segmental bronchi. In stage IV NSCLC cancer, studies have shown the development of distant metastases in extrathoracic organs. For each organ, percentages indicate the prevalence of metastases in lung squamous cell carcinoma and adenocarcinoma. 70% of individuals diagnosed with lung cancer present with advanced stage disease (stage III or IV)[6].

Recent whole-genome sequencing has revealed the most prevalent genetic alterations involving tumor suppressor genes. Most tumor suppressor genes require the loss or inactivation of both alleles to promote tumor development. As a result, replacing just one functioning allele may be enough to restore normal growth regulation and cause tumor death. P53 and TUSC2 are the two potential genes[4].

2. P53

The tumor suppressor gene p53 is the most commonly mutated in NSCLC[4,7]. P53 is a transcription factor that promotes apoptosis while suppressing pro-survival genes. P53 functions as a transcription gate that regulates DNA damage or oncogenic activity, stopping the cell cycle in the G1 phase to permit DNA repair or, starting apoptotic self-destruction if the changes are permanent[4].

Cancer cells with mutant or faulty P53 proteins are expected to be resistant to treatment since standard chemotherapy and radiation therapy induce DNA damage. However, it is unclear whether simply modifying the P53 protein by adding wild-type

p53 to the cancer cell genome is sufficient to produce apoptosis because neoplastic cells contain many somatic mutations. In studies, apoptosis was triggered by replacing defective/absent p53 with wild-type p53 in many tumor cell types. The discovery that reintroducing wild-type p53 into non-small cell lung cancer cell lines with mutant or deleted p53 can induce apoptosis established the foundation for further research into the therapeutic potential of this protein. Some p53 alterations, known as gain-of-function mutations, may confer oncogenicity on p53. The first p53 gene replacement was accomplished using retroviral vectors, and functional restoration of p53 was shown to suppress the growth of various human NSCLC cell lines in vitro. Intratumoral p53 gene therapy with this retroviral vector inhibited tumor development in several human NSCLC models with p53 loss or mutation. This research proved for the first time how reinstating a single tumor suppressor gene in vivo can promote tumor regression[4].

Studies related to p53 have shown that targeted gene replacement of tumor suppressor genes can lead to cancer regression[4]. Gene therapy is one of the different approaches to targeting P53[7].

3. TUSC2

Allele loss and genetic alterations in the third chromosome's short arm are the most common genetic aberrations in human cancers, including lung. Findings suggest that the 3p21.3 region of third chromosome contains one or more putative tumor suppressor genes that operate as "gatekeepers" in the molecular etiology of lung cancer. In vitro studies show that the 3p21.3 genes demonstrate varied degrees of tumor suppression, with the tumor suppressor candidate 2 gene (TUSC2) displaying the most suppressive effect. TUSC2 protein is absent in most NSCLC cell lines lack. TUSC2 expression was the most pro-apoptotic in human NSCLC cells among candidate genes for the tumor suppressor 3p21.3. Its direct interaction with a type of protein found in NSCLC cells called Apaf-1 causes apoptosis. Apaf-1 plays an important role in mitochondria-dependent apoptotic pathways. These Apaf-1 proteins appear to be functionally inactive, as evidenced by the lack of ATPase activity. Forced expression of TUSC2 in TUSC2-deficient tumor cells led to the release of cytochrome c from mitochondria into the cytosol, allowing TUSC2 to bind Apaf-1, recruit it to key cellular sites, activate Apaf-1, and induce apoptosis[4].

Therefore, considering that both gene therapy options show a safe clinical response, the combination of these methods with other NSCLC treatments deserves to be investigated[4].

Another item to consider is that systemic metastasis is the main cause of death in patients with NSCLC. In this case, by encapsulating the plasmid with nanovesicles, gene therapy drugs can be administered intravenously to the most distant metastases[4].

4. Conclusions

Maintaining human health due to various diseases is a great concern all over the world. Lung cancer is one of the world's worst and most prevalent diseases. Biotechnology scientists rushed to help doctors by providing new treatment methods for cancer, such as gene therapy.

5. References

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